IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

MEHLHORN, Rolf Joachim

Serial No.: 10/759,222

Filed: 20 January 2004

For: METHOD FOR LOADING LIPID LIKE VESICLES WITH DRUGS OR OTHER CHEMICALS

Group Art Unit: 1614

Examiner: Kevin E. Weddington

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Dear Sir:

This Reply Brief is submitted in response to the Examiner's Answer, mailed 17 March 2010.

STATUS OF CLAIMS

The current status of the claims is:

Claims 1-26 are pending.

Claims 13-15 and 24-26 have been withdrawn by the examiner.

Claim 1-12 and 16-23 stand rejected are the subject of this appeal.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejection to be reviewed in this appeal are:

1. **This ground for rejection has been withdrawn by the examiner.** The rejection was directed to whether claims 1-8, 10-12 and 16-23 contain subject matter that was not described in the specification is such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention (written description rejection).

2. Whether claims 1-12 are unpatentable over Nichols, et al., Catecholamine Uptake and Concentration by Liposomes Maintaining pH Gradients, Biochimica et Biophysica Acta, 1976, 455:269-271 (Evidence Appendix, Exhibit "A"), Deamer, et al., The Response of Fluorescent Amines to pH Gradients Across Liposome Membranes, Biochimica et Biophysical Acta, 1972, 274:323-335 (Evidence Appendix, Exhibit "B"), or Cramer, et al., NMR Studies of pH-Induced Transport of Carboxylic Acids Across Phospholipid Vesicle Membranes, Biochemical and Biophysical Research Communications, 1977, 75:295-301 (Evidence Appendix, Exhibit "C").

3. Whether claims 16-23 of the instant application are patentably distinct from claims 1-7 of U.S. Pat. No. 5,762,957 for if they are, then the examiner has rejected the claims under the judicially created doctrine of obviousness-type double patenting.

ARGUMENT

Applicant acknowledges and thanks the examiner for the withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

Claims 1-12 are patentable over Nichols, et al., Deamer, et al. or Cramer; i.e., none of these references renders the claimed invention obvious

The crux of the examiner's rejection revolves around the fact that Nichols< Deamer and Cramer all teach the creation of a pH gradient between inside and outside a liposome and the subsequent loading of substances into the liposome as the result of that gradient. This, however, as is pointed out numerous times in appellants responses – and ignored by the examiner – **is not the invention of the instant application**, as is amply pointed out in the Appeal Brief and, for the sake of brevity, will not be iterated her in its entirety.

That is, the Board's attention is respectfully directed to Appeal Brief wherein it is stated;

> With regard to Nichols, the examiner's position is that it does teach the loading of an amine into a liposome using a pH gradient. This appellant does not dispute. The crux of the current invention, as was pointed out to the examiner on several occasions, is that the concentration of the loaded amine – or of any basic or acidic chemical substance – can be maintained in the lipid-like vesicle, i.e. liposome, for a substantial period of time after the pH gradient has been destroyed. This is an unexpected, surprising, utterly novel development that in no way could have been gleaned from Nichols by those skilled in the art. In fact, Nichols says nothing whatsoever about what happens to the loaded material after loading. (Appeal Brief, page 10)

The situation is exactly the same with regard to Deamer (Appeal Brief, pages 10-11) and Cramer (Appeal Brief, page 11). None of the references cited by the examiner teaches, suggests, motivates or in any manner so much as tangentially suggests the instant invention to the skilled artisan. None of Nichols, Deamer and/or Cramer in any combination renders the instant invention obvious.

Double patenting rejection

Applicant apologizes for not addressing the double patenting rejection in the Appeal Brief.

Applicant is prepared to submit a terminal disclaimer disclaiming any term of a patent that issues based on the instant application should such terminal disclaimer be all that stands between this applicant and issuance.

Unintentional error

Appellant has noticed that claim 16 was inadvertently omitted from the Claims Appendix. The Claims Appendix is thus resubmitted herewith to correct the oversight.

CONCLUSION

Clearly, Nichols, Deamer and Cramer do not render the instant invention obvious. In fact, the examiner has not even addressed the true invention and thus has failed utterly, as a matter of law, to establish a *prima facie* case of obviousness. Appellant therefore respectfully restates his request that the Board reverse the examiner's rejection and order that the application be passed to issue.

Date: 11 May 2010

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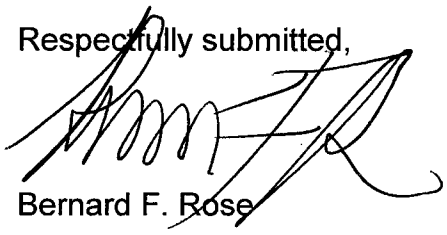
Respectfully submitted,



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CLAIMS APPENDIX

The claims on appeal are:

1. A method of loading lipid-like vesicles, comprising:

forming lipid-like vesicles in a solution comprising an acidic buffer if the chemical species to be loaded is basic or a basic buffer if the chemical species to be loaded is acidic; wherein:

membranes of the formed lipid-like vesicles are impermeable to the buffer;

adjusting the pH of the solution exterior to the membranes of the lipid-like vesicles to a basic pH if the chemical species to be loaded is basic or to an acidic pH if the chemical species to be loaded is acidic;

adding a basic chemical species to the adjusted basic exterior solution or an acidic chemical species to the adjusted acidic exterior solution;

loading the chemical species into the vesicle; and

adjusting the exterior solution to a physiologically benign pH; wherein:

the chemical species is substantially maintained in the vesicle for at least one quarter hour after the adjustment of the exterior solution.

2. A method of loading lipid-like vesicles having a membrane permeable to a chemical species to be loaded and for substantially maintaining the loaded chemical species within the vesicle for at least one-quarter hour following loading by inducing a pH gradient across the membrane, comprising:

(1) incorporating within the vesicle a buffer solution buffered to a selected acid or alkaline pH having a selected molarity and at least one selected pKa approximately equal to the selected buffer pH, the membrane being substantially impermeable to the buffer for at least one-quarter hour following loading of the chemical species;

(2) positioning the vesicles in a bulk solution having a selected pH; and

(3) providing the bulk solution with a chemical species having one or more selected acid pH responsive groups if the buffer is alkaline or one or more basic pH responsive groups if the buffer is acidic wherein the pH of the bulk solution is

at least 0.5, 0.3 or 0.2 of a pH unit higher than the pH of the buffer if the buffer is acidic and the chemical species has one, two, or three or more basic pH responsive groups, or the pH of the bulk solution is at least 0.5, 0.3 or 0.2 of a pH unit lower than the pH of the buffer if the buffer is basic and the chemical species has one, two or three or more acid pH responsive groups, the pH responsive groups of the chemical species having one or more acid pH responsive groups have a pKa that is generally lower than or equal to the pH of the bulk solution and generally higher than or equal to 3.5 and the pH responsive groups of the chemical species having one or more basic pH responsive groups have a pKa that is generally higher than or equal to the pH of the bulk solution and generally lower than or equal to 11.

3. A method according to claim 2 wherein the pH responsive group or groups are acid pH responsive groups and the buffer has a pKa of about 10.

4. A method according to claim 3 wherein the chemical species has a pKa of about 4-7.

5. A method according to claim 4 wherein the pH responsive group is a carboxyl group.

6. A method according to claim 2 wherein the pH responsive group or groups are basic pH responsive groups, and the buffer has a pKa in the range of about 5.

7. A method according to claim 6 wherein the chemical species has a pKa from about 7-10.

8. A method according to claim 7 wherein the pH responsive group is an amino group.

9. A method according to claim 8 wherein the chemical species is an amine.

10. A method according to claim 2 wherein the vesicle is prepared in the buffer and incorporates the buffer via mixing and sonication.

11. A method according to claim 2 wherein the pH of the bulk solution is about 7.0 to about 7.8.

12. A method according to claim 11 wherein the pH of the bulk solution is about 7.4.

16. A kit for loading lipid-like vesicles having a membrane permeable to the chemical species to be loaded comprising:

(1) a first compartment having a first solution having membranous lipid-like vesicles incorporating a buffer buffered to a selected acid or basic pH, the buffer having at least one selected pKa approximately equal to the selected buffer pH and a selected molarity and being substantially impermeable to the vesicle's membrane for at least one-quarter hour following loading of the chemical species and the first solution having a selected pH such that the stability of the vesicle and its buffer can be maintained for a period of at least one week at 4 °C.

(2) a second compartment, separate from the first compartment, having a second solution having a selected pH;

(3) a chemical species permeable to the vesicle having a selected pKa and one or more selected acid pH responsive groups if the buffer is basic or one or more basic pH responsive groups if the buffer is acidic, the chemical species being initially present in a selected one of two solutions with the second solution having a pH such that a mixture of the first and second solutions would have a pH at least 0.5, 0.3, or 0.2 of a pH unit higher than the pH of the buffer if the buffer is acidic and the chemical species has one, two, or three or more basic pH responsive groups at least 0.5, 0.3 or 0.2 of a pH unit lower than the pH of the buffer if the buffer is basic and the chemical species has one, two or three or more acid pH responsive groups, the pH responsive groups of the chemical species having one or more acid pH responsive groups have a pKa that is generally lower than or equal to the pH of the mixture of the first and second

solution and generally higher than or equal to 3.5 and the pH responsive groups of the chemical species having one or more basic pH responsive groups have a pKa that is generally higher than or equal to the pH of the mixture of the first and second solutions and generally lower than or equal to 11.

17. A kit as set forth in claim 16 wherein said chemical species is a drug.

18. A kit as set forth in claim 17 wherein the mixture will have a pH that is physiologically benign in regard to the blood of a mammal.

19. A kit as set forth in claim 18 further comprising means for parenterally delivering the mixture to a mammal in vivo.

20. A kit for loading lipid-like vesicles having a membrane permeable to an acid or basic chemical species to be loaded comprising:

(1) a first compartment having a first solution having membranous lipid-like vesicles incorporating a buffer buffered to a selected basic pH if the chemical species to be loaded is an acid or acid pH if the species in a base, the buffer having a selected pKa and a selected molarity, the membrane being substantially impermeable to the buffer for at least one-quarter hour following loading of the chemical species, the first solution having a selected pH such that the stability of the vesicle and its buffer will be maintained for a period of at least one week at 4 °C;

(2) a second separate compartment having a first substance which when combined with the first solution will adjust the pH of the first solution so as to provide a predetermined pH gradient between the buffer within the vesicle and the pH adjusted first solution; and

(3) a third separate compartment having a second substance which when combined with the pH adjusted first solution will further change the pH of said solution to a physiologically benign value with regard to the blood of a mammal.

21. A kit as set forth in claim 20 further comprising a selected chemical species.

22. A kit as set forth in claim 21 wherein the selected chemical species is a drug.

23. A kit as set forth in claim 22 further including a means for parentally delivering the vesicle solution having the physiologically benign adjusted pH to a mammal in vivo.

24. A method of detoxifying an animal suffering from an overdose of a chemical species with basic pH responsive groups comprising injecting the animal with a solution having a physiologically benign pH with respect to the animal, the solution having large volumes of liposomes having a buffer solution buffered to a pH generally lower than or equal to 5.4 and the buffer having at least one selected pKa and a selected molarity within the physiological range of the animal the liposomes being substantially impermeable to the buffer for at least one hour after injection.